Based on laboratory experiments and field observations by the Hooper Foundation extending over more than two years, the following possibilities seem most likely. The mussel poison is a metabolic product which may be elaborated in excessive amounts either during the spawning period or after ingestion of a particular kind of food. In addition to this it is not unlikely that the meteorological and the tidal conditions are of considerable importance as secondary factors. Another view holds that the toxin is preformed in the water, originating possibly from poisonous animals or from decomposition of vegetable matter, and is absorbed and stored in the shellfish. Hypotheses which are based on the assumption of bacterial decomposition, copper salts, pollution of the water, etc., as causative factors, are not supported by actual observations.

A noteworthy feature of the 1929 outbreak is the fact that clams from various localities of the coast were equally as poisonous as the mussels. Of the eight varieties tested in the laboratory, five kinds of clams which are commonly used as food were found highly toxic. One sample of oysters and several abalones proved harmless.

It has again been noticed that the digestive organ ("liver") of the shellfish yields by far the most potent poison. Extraction of mussels' livers with methyl alcohol has given a crude substance which is lethal to mice in doses of 0.1 milligram on intrap. injection. It is evident, therefore, that we are dealing with a very deadly poison, comparable in strength to some of the most poisonous alkaloids.

Although regular observations along the California coast have been made only for three consecutive summer seasons the epidemiological facts and the laboratory findings thus far accumulated fully warrant the establishment of a strict quarantine on all bivalves during the summer months.

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J. H. Kuser, M. D. (6 Cheda Building, San Rafael). Doctor Enright's most complete and extensive report on clam and mussel poisoning certainly deserves study by the medical profession.

On July 22, 1929, six cases of mussel poisoning were reported to my office. Mussels were gathered under water and had never been exposed to low tide. All who were poisoned recovered after washing of the stomach. It was fortunate that two medical men were present who gave efficient first aid. One patient was taken to the hospital for treatment. After ten days she was allowed to return to her home. She was extremely prostrated and toxic.

This office was informed that on August 5 three deaths occurred after eating Tomales clams. None of these cases came under our personal observation. The State Department of Public Health quarantined promptly all clams and mussels from Sonoma and Marin counties. Specimens of mussels and clams were at stated intervals submitted to the Hooper Research Laboratories. All were found toxic until the middle of October. The last shellfish were submitted on October 31, when they were found not toxic. Quarantine was raised on November 2, 1929.

A peculiar condition was that oysters in the upper portion of Tomales Bay were found nontoxic by the laboratory. These specimens, as well as abalones, were gathered at the same time, on August 16, 1929.

Taking into consideration the extreme toxicity of these shellfish during certain periods of the warm summer months and that no specific therapy for combating the poison has yet been found, and the impossibility of distinguishing poisonous from nonpoisonous mussels or clams, it would seem advisable that the state authorities establish a closed season for clams and mussels in those months during which they have been found poisonous by the Hooper Research Laboratory.

THE IMMUNOBIOLOGIC REACTION IN TUBERCULOSIS*

WITH REFERENCE TO INFANCY AND CHILDHOOD

By Roy E. Thomas, M. D.
Los Angeles

Discussion *by F. M. Pottenger, M. D., Monrovia; Robert A. Peers, M. D., Colfax; Harold K. Faber, M. D., San Francisco.*

TWO infants are exposed to tuberculosis. Why does one develop clinical disease while the other does not?

Of two children who have developed clinical tuberculosis and who are living under the same conditions, one dies and the other recovers. Why is this so? The answer to both questions is probably to be found in the study of the subject as indicated by the caption of this paper.

MAJOR FACTORS TO BE CONSIDERED

Primary Infection.—This may occur at any age, but probably takes place very early in infants exposed daily to open cases of tuberculosis, as in cases in which the mother, father, or both are tuberculous. Of one hundred and twenty-four tuberculous infants observed by Bernard[1] the mother had tuberculosis in ninety-five instances, the father in twenty, and both father and mother in twenty.

The route of infection in the great majority of cases is probably through the respiratory tract by inhalation of bacillus-laden dust particles or droplets.

The Tubercle.—When tubercle bacilli gain entrance to susceptible tissue for the first time a tubercle results, the formation of which has been so beautifully described by Krause[2] in his article, "The Anatomical Structure of the Tubercle."

If an experimental inoculation of virulent bacilli is made in a convenient site, such as the skin or cornea, nothing is to be seen for nearly a week. Then a pale, firm nodule appears which slowly enlarges. About the third week this nodule becomes irregular in shape, its center becomes yellowish white in color, and induration gives place to a doughy consistence. While these changes are occurring, the zone of tissue immediately surrounding the nodule has assumed a pinkish color. At the same time small secondary nodules may appear on the edges of the primary nodule. The appearance of these secondary signs indicates the termination of what Krause calls the preallergic phase of tuberculosis. Primary tubercle develops without signs of inflammation.

A microscopic study of the primary tubercle shows surrounding each bacillus or group of bacilli a collection of epithelioid cells. These characteristic cells are arranged in roughly concentric layers which become flattened toward the periphery, where interlacing fibrils appear. Often near the center of this spherical collection of cells

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are found large multinuclear cells called "giant cells," which probably represent degenerated epithelioid cells. The other cell usually present in the elementary tubercle is the lymphocyte, found in greatest numbers near the periphery and evidently an invader, in contrast to the epithelioid cell which is apparently derived from the multiplication of cells at the site of the inoculation.

It will be evident from this brief description of the formation of the primary tubercle that tuberculosis, previous to the occurrence of the phenomenon we call allergy, is strictly a proliferative process.

The Allergic Reaction in Tuberculosis.—Allergy has been defined by Kolmer [3] as a state of altered reactivity of the body cells—usually an exaggerated susceptibility, but it may indicate reduced susceptibility or tolerance.

Zinsser [4] says: "All forms of specific hypersensitiveness are probably based on the same fundamental mechanism, namely, an acquired altered capacity of the cells to react to the particular inciting substance."

In tuberculosis a state of allergy follows the formation of primary tubercle, whether this results from the implantation of living or dead bacilli. An allergic reaction is the response to the implantation in tissue then in the allergic state, of tubercle bacilli, living or dead, or the injection of tuberculin.

This response is characterized by exudation. It is, then, the allergic reaction which causes all tuberculous inflammation, resulting in infiltration, consolidation or effusion, according to the location involved. It follows that all clinical signs and symptoms are dependent upon this phenomenon.

Endogenous Reinfection.—This occurs to some degree in all cases of active tuberculosis. Bacilli reach new fields through the lymphatics, through the blood stream and by direct contact. At once the protective allergic reaction begins, not only at the point of reinoculation, but also about every other focus of infection in the body. If these reactions are not too severe and not too frequent they stimulate sufficient proliferation to wall off all foci and thus effect a cure. Allergic reactions may be so severe as to result quickly in death or so mild that no clinical evidence of them is apparent at the time.

Tuberculoimmunity.—Immunity in tuberculosis is defined by Krause [5] as that condition of increased specific resistance to implantation and extension of tubercle bacilli which comes into existence with the earliest formation of the anatomical tubercle. If we accept this conception it is evident that immunity begins with the allergic state and that both continue as long as tubercle bacilli continue to be present in the individual. Indeed, the only distinction between allergy and immunity is that the allergic response is an attribute of the local cell while immunity is an acquired characteristic of the body as a whole.

Practically speaking, immunity has to do chiefly with exogenous reinfection. In experimental animals reinoculation results in a well localized and chronic lesion which seldom causes death. In those cases which do end fatally, the progress of the disease is exceedingly slow.

Exogenous Reinfection.—Does adolescent tuberculosis result from endogenous reinfection from a focus occurring in infancy, or is it an exogenous reinfection in an individual whose childhood immunity has become impaired from one cause or another? It is probable that both occur. It is also very likely that a rare case of primary infection occurs in the adult. Lawrason Brown [6] believes that adult pulmonary tuberculosis results from exogenous reinfection between the ages of fifteen and twenty in approximately 30 per cent of cases.

Production of Immunity as a Therapeutic or Prophylactic Measure.—Of what practical value is our imperfect knowledge of allergy and immunity in tuberculosis? Attempts to produce a passive tuberculoimmunity have failed because the immune reaction is cellular and not humoral. The active immunization of infants with living bacilli (Calmette's B. C.-G.) is now being tried on rather a large scale in France and elsewhere, but is still in the experimental stage.

SUMMARY

Primary infection usually occurs in infants exposed to open cases of tuberculosis in their homes. It occurs chiefly by inhalation. Its first manifestation is the primary tubercle, developed by proliferation of the characteristic epithelioid cell. Following this preallergic phase occurs the allergic state, upon which all inflammatory reaction depends, and tuberculoimmunity which largely determines the clinical course of the disease. I have tried to show that the development of the tubercle is a proliferative process exclusively; that exudation is an allergic reaction which, although at times the direct cause of most alarming symptoms, is in reality a defensive phenomenon.

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2. Krause: Am. Rev. of Tuberculosis, February, 1927.
3. Kolmer: From an address delivered before the American Association for the Study of Allergy, Minneapolis, Minn., June 11, 1928.
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DISCUSSION

F. M. Pottenger, M. D. (Monrovia).—Dr. Thomas's paper sets out the early immunological reactions in tuberculosis in a very clear manner.

In order to understand tuberculosis as a clinical disease it is necessary to understand what takes place at the time of the primary infection. The primary infection soon sensitizes all body cells to tuberculoprotein, so that when they come in contact with it again they are resistant. This resistance shows itself in many ways, the most evident of which is an inflammatory reaction. This inflammatory reaction is a very important factor in the prevention of the spread of bacilli through the tissues. It has a tendency to hem them in wherever they are deposited and to prevent them from going farther until they are either destroyed or are encapsulated.

As a result of this allergic reaction, bacilli of reinoculation are for the most part held at the point of implantation, and if the numbers are relatively small the infection which takes place usually proves to be abortive. This is probably the greatest defensive factor that we have in chronic tuberculosis during the early period of dissemination.

It is probable that immunity is something different from sensitization of cells and allergy; at the same time it is also probable that sensitization and allergy are states which are a part of, which precede and which lead up to the ultimate establishment of immunity.

Primary infection of the lung is necessarily of exogenous origin. It may be that the bacilli enter through the air passages, or through the gastrointestinal tract. The theory of the former method has the most adherents; but those who adhere to the latter call attention to the fact that if bacilli gain entrance to the body through the alimentary canal and pass through the intestinal wall, they immediately enter the lymph channels, are poured into the thoracic duct, and thence into the subclavian vein going to the heart, and on through the lesser circulation. So the first opportunity for implantation would be in some portion of the lesser circulation. Entering virgin soil, as the bacilli which form the primary inoculation do, they meet no specific tissue resistance; but entering immune soil, as the bacilli of reinoculation do, they meet the resistance produced by cell sensitization, and a tissue response in the form of allergic inflammation. This protection becomes so great after infection has been present for some time that bacilli can enter the tissues from without only with great difficulty, or when the specific protection has been lowered. So after infection has once taken place the endogenous source of inoculation is much more plausible than the exogenous.

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Robert A. Peers, M. D. (Colfax).—Doctor Thomas, in his paper, and Doctor Pottenger, in the discussion, have covered the fundamentals of the cellular reaction to first and to subsequent invasions of tubercle bacilli. Further discussion of the point would lead merely to elaboration of details.

In considering, however, the two questions which Doctor Thomas formulates at the beginning of his paper, one must recognize other factors involved besides those of allergy or immunity. True, there is in all of us a certain amount of natural immunity, a greater or lesser amount of inherited cellular, or humoral immunity, or both, which gives each of us greater or lesser resistance to the invasion, and to the multiplication and extension to other parts of the organism of the tubercle bacillus. This natural immunity or lack of immunity is undoubtedly a factor in the determination of which infected child develops clinical tuberculosis, and also in the determination of which of those with clinical tuberculosis will fail to recover.

Again the question of dosage plays a part in the outcome of the process which follows implantation. A large dose of bacilli received from the careless tuberculous father or mother is, other things being equal, more dangerous to the child than a small dose of bacilli. Many bacilli furnish the exciting cause for many primary tubercles in first infections. Many bacilli, in secondary infections, furnish the medium for many isolated foci of allergic response. Immunity is a relative term. The greater the dosage of bacilli the more probable this immunity will be overcome.

Accident, as Krause has pointed out, also plays a part in the determination of the result of infection. Some tissues are more suited to hold and fix the bacilli than are others. Thus the accident of location of the first tubercle plays quite a part in retention or extension. The same is true in secondary infection whether endogenous or exogenous. The accident of the rupture of a solitary caseating lymph node into a blood vessel or into the thoracic duct with the production of an acute miliary tuberculosis may furnish the answer to these questions. Or again, the accident of extension to the meninges of the brain and cord of an already allergic child causes symptoms and results due to the allergic response of exudation quite different from those experienced in the more fortunate individual whose allergic response occurs in the lungs.

As Doctor Pottenger states truly, "In order to understand tuberculosis as a clinical disease it is necessary to understand what takes place at the time of the primary infection."

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Harold K. Faber, M. D. (Stanford University Medical School, San Francisco).—Discussion of the subject of Doctor Thomas's paper would be incomplete without mention of three common clinical manifestations of immunobiologic reaction to tuberculosis—erythema nodosum, phlyctenular keratoconjunctivitis, and the so-called epituberculous lesion of the lung. All these coincide in a large majority of cases with a period of violent reactivity to tuberculin, and are regarded by good authorities as effects of tuberculin itself. The literature on erythema nodosum in relation to tuberculosis is quite extensive. The work of Ernberg [1] and of Wallgren [2] may be cited. Casparis [3] has recently discussed the relation of phlyctenular lesions to tuberculosis. Eliasberg and Neuland's [4] paper may be consulted for a discussion of the epituberculous infiltrations of the lung. Another paper of Wallgren's [5] discusses the clinical manifestations of tuberculin allergy in infants and children in considerable detail.

It has perhaps been too seldom appreciated by the medical profession at large that the development of allergy to tuberculin is accompanied in many instances by rather stormy symptoms and fairly characteristic signs or radiographic changes, which can often be recognized by careful study, and Doctor Thomas, in calling attention to the fact, is performing a useful service.

1 Jahrb. f. Kinderheilk., 1921, 95, 1.
2 Jahrb. f. Kinderheilk., 1927, 117, 313.
3 Am. Jour. Dis. Child., 1927, 34, 779.
4 Jahrb. f. Kinderheilk., 1921, 94, 102.
5 Am. Jour. Dis. Child., 1928, 36, 702.

FREE FASCIAL GRAFTS—THEIR UNION WITH MUSCLE*

REPORT OF CASES

By S. L. Haas, M. D.
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Discussion *by John Hunt Shephard, M. D., San Jose; Leo Eloesser, M. D., San Francisco; Sterling Bunnell, M. D., San Francisco.*

A NUMBER of operative procedures, particularly the cure of hernia, depend upon the principle that fascia will unite with muscle.

OBSERVATIONS OF SEELIG AND CHOUKE

In spite of the large number of successful hernia operations, Seelig and Chouke [1] concluded from their observations on recurrences after herniotomy that fascia will not unite with muscle. To further substantiate their claims they performed a series of experiments on animals in which they reduplicated the fascia lata to simulate Poupart's ligament and sutured the edge of the turned flap to the underlying muscle. In

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